Findings from CRU Review of Pro000095555

OBJECTIVE AND BACKGROUND

This report presents findings from a review of Pro00009555, which focused primarily on: (1) documenting eligibility criteria of all randomized participants and (2) comparing collected data to the IRB approved protocol and informed consent form (ICF).

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Pro00009555 is a two-arm randomized clinical trial (RCT) comparing escitalopram to PBO in patients with stable ischemic heart disease (IHD) and mental stress-induced myocardial ischemia (MSIMI). The principle investigator (PI) is Wei Jiang, MD.

SCOPE OF PARTICIPANT ELIGIBILITY REVIEW

Although a total of N=307 patients completed the REMIT baseline screening and had eligible echocardiographic assessments of MSIMI, the review of participant eligibility focused only on confirming whether those randomized (N=127) to the REMIT RCT met all of eligibility criteria. To accomplish this task, the case report binders and, if necessary, medical records of all randomized participants were examined.

A summary of the IRB Approved REMIT Inclusion and Exclusion Criteria are presented in **Table 1**. To be eligible to participate in the trial, all participants had to meet 3 Inclusion Criteria (IC) and none of the 12 Exclusion Criteria (EC).

Table 1. REMIT Study IRB Approved Inclusion and Exclusion Criteria

No.	Inclusion Criteria
1	Age 21 or greater
2	Stable IHD
3.0	BDI score ≥ 5 (Valid until Oct 2007)
3.1	BDI score ≥ 4 (Valid until Oct 2008)
3.2	BDI score no longer part of the inclusion criteria (Valid after Oct 2008)
No.	**Exclusion Criteria**
1	Recent myocardial infarction, coronary artery bypass graft surgery, or other revascularization procedures (≤ 3 months)
2	LVEF < 15% measured by echocardiography, RNV, or cardiac catheterization
3	Life threatening arrhythmia or arrhythmia interrupting the interpretation of ischemia

Table 1. REMIT Study IRB Approved Inclusion and Exclusion Criteria	
No.	**Inclusion Criteria**
4	Unable to withdraw from anti-anginal medications during ischemic assessment phase
5	Unable to perform exercise testing
6	Pregnancy
7	Current or previous history of bipolar disorder, cyclothymia, schizophrenia, schizoaffective or schizophreniform disorder, or other psychotic disorders
8	Active suicidal ideation
9	Current substance abuse or history of substance abuse in the previous 6 months
10	Significant cardiac, pulmonary, metabolic, renal, hepatic disease, or malignancy, interfering with patient's participation in this study
11	Seizure (history and/or present) with/without treatment
12	Currently taking antidepressants that cannot be discontinued

SUMMARY OF ELIGIBILITY FINDINGS

From a total sample size of 127, 26 (or 20.5%) of the randomized patients did not meet one or more eligibility criteria listed in **Table 1**. (Note: This is a conservative estimate as it does not count among those ineligible those patients who started but failed to complete the exercise stress test, which is relevant to EC 5. See Table 5 on page 6 for a list of reasons why these patients were not counted among those ineligible.)

Of the 26 participants who did not meet all eligibility criteria, 22 (84.6%) failed to meet only one criterion and 4 (15.4%) failed to meet two criteria. **Table 2** lists the eligibility criteria that failed upon review, the total number of participants who failed each criterion, and the corresponding participant IDs.

Table 2. A Summary of the Number of Participants that Failed by Eligibility Criteria		
Eligibility Criteria	**Number of Participants**	**Participant IDs**
EC 1	N = 1	090-024
EC 4	N = 10	161-049; 175-054; 206-066; 233-077; 235-080; 238-082; 264-089; 299-098; 310-105; 358-115
EC 5	N = 6	020-004; 046-016; 102-029; 180-051; 236-081; 377-121
EC 6	N = 3	109-033; 319-103; 379-122
EC 10	N = 1	025-012
EC 12	N = 1	144-042
IC 3.1 and EC 4	N = 1	015-003

EC 4 and EC 5	N = 2	268-093; 284-095
EC 6 and EC 12	N = 1	265-090

Note: EC = Exclusion Criteria; IE = Inclusion Criteria.

Table 3 provides detailed information regarding the reasons why a participant was marked as failing that specific eligibility criterion.

Table 3. Reasons for Not Meeting Eligibility Criteria

Eligibility Criteria	Participant ID	Reason for Not Meeting Criteria
EC 1	090-024	Patient had a cardiac catheter and unstable angina in the last 3 months as per the 1st week of July discharge summary.
EC 4	161-049	Patient had a defibrillator and was not able to hold beta blockers due to safety reason (mention in ECHO note, baseline visit). On consent note, it says "patient is on beta blockers but their doctor did NOT permit to discontinue. Pt will be tested on Beta blockers."
EC 4	175-054	Patient is on metoprolol - no documentation was found that confirmed that the beta blocker will be held for the study period.
EC 4	206-066	Patient did not hold metoprolol - which is a beta blocker.
EC 4	233-077	The note says that the patient did not hold beta blockers.
EC 4	235-080	As per the notes, patient did not want to withdraw from the beta blockers for the baseline testing
EC 4	238-082	As per the notes, patient did not hold their beta blockers.
EC 4	264-089	The patient was on beta blockers; no information or documentation was found noting whether or not the beta blockers were stopped. The patient dropped out before starting any study meds – as per the participant binder the patient was on any study meds.
EC 4	299-098	The patient did not hold his beta blocker because he forgot. The visit was conducted as planned. The patient died on 12/1/2010. Week 5 phone visit was Nov 4th. Finished 6 weeks. The study team became aware of the death on 3/29/11 as the print out of the obituary is dated 3/29/11. They officially noted this at the 1-year follow-up on 9/23/2011. He was in the follow-up phase when he died. The death was not reported to the IRB. Cause of death cannot be determined as there is no documentation. The patient was 68 years old at the time of death.
EC 4	310-105	There are 2 notes in participant binders, stating patient was not off of the beta blockers.
EC 4	358-115	As per the study team's documentation - the subject did not hold the beta blockers.

Table 3. Reasons for Not Meeting Eligibility Criteria		
Eligibility Criteria	**Participant ID**	**Reason for Not Meeting Criteria**
EC 5	020-004	Unable to perform exercise stress test. Patient could not walk very well per notes.
EC 5	046-016	Unable to perform exercise stress test. Patient had bilateral hip replacement. Arrived in wheelchair.
EC 5	102-029	Unable to perform exercise stress test. Patient had aortic dissection. Cardiologist said no to stress test.
EC 5	180-051	The stress test was not done as the patient had a left ventricular aneurysm - that was new.
EC 5	236-081	Unable to perform exercise stress test. Patient walked with a cane.
EC 5	377-121	The subject declined the exercise test. No reason given.
EC 6	109-033	Patient was in her early 50s during the time of the study. We looked in the EMR and could not confirm the WOCBP status. There was no pregnancy test done to rule out pregnancy. No documentation of hysterectomy or amenorrhea.
EC 6	319-103	Patient less than 55 years of age at the time of the study. No comments found on her regarding WOCBP status. There was no pregnancy test done to rule out pregnancy.
EC 6	379-122	Patient is 48 years of age and has 2 children (ages 5 and 9). No documentation on childbearing status or any pregnancy were found. We looked in EMR as well - no documentation found.
EC 10	025-012	Did not meet criteria due to history of lung cancer which metastasized to the brain. The patient dropped out due to cancer spreading to the brain and did not get study intervention.
EC 12	144-042	As per study notes, patient had depression and takes daily amitriptyline. The participant source documents by the CRC mention that the patient plans to discontinue amitriptyline, but we did not find any documentation confirming this (med logs etc.). We cannot confirm if it was a current med list form the notes.
IC 3.1 and EC 4	015-003	We did not find the BDI score source document, only CRF found. We did not find documentation for beta blocker discontinuation.
EC 4 and EC 5	268-093	Patient did not perform exercise test because he had a stroke approximately 3 years earlier and is in a wheelchair since. Patient is also diabetic and had foot ulcers so could not do the Exercise test. Patient did not stop beta blockers per Dr. Jiang's instructions.
EC 4 and EC 5	284-095	The patient refused to hold beta blockers and did not do the exercise stress test due to PAD (Peripheral Artery disease).

Table 3. Reasons for Not Meeting Eligibility Criteria		
Eligibility Criteria	**Participant ID**	**Reason for Not Meeting Criteria**
EC 6 and EC 12	265-090	Patient was admitted for chest pain 2 weeks prior to randomization. Patient found to be depressed during hospitalization and started on fluoxetine prescribed by Dr. Jiang. After discharge, she remained on fluoxetine. She is also a WOCBP, but no pregnancy test was completed and she does not have a hysterectomy or any other permanent contraception.

SUMMARY OF QUESTIONABLE FINDINGS

As noted earlier, N = 6 patients were rated as having met all eligibility criteria by study team despite having an incomplete exercise stress tests (EC 6; Unable to perform exercise testing). **Table 4** lists each of these 6 patients and provides a brief rationale as to why these patients were determined to have passed eligibility criteria by the CRU review team even though they were unable to finish the exercise stress test.

Table 4. Questionable Participant Eligibility	
Participant ID	**Reason for Not Meeting Criteria**
071-057	Was on the treadmill although couldn't keep up, but was on the treadmill for 2 minutes. We concluded that the patient met criteria as they were on the treadmill and data was obtained. We rated this patient as able to perform the test.
100-027	Unable to perform exercise test. Patient was unable to keep up with the treadmill and reported fatigue, had high BP dyspnea not on beta blockers. We concluded that the patient met criteria as they were on the treadmill and data was obtained. We rated this patient as able to perform the test.
101-028	Stress test terminated early. Patient had non-sustained V-tachycardia. We concluded that the patient met criteria as they were on the treadmill and data was obtained. We rated this patient as able to perform the test.
106-032	Unable to complete the stress test. Test was stopped early due to hypertensive response. We concluded that the patient met criteria as they were on the treadmill and data was obtained. We rated this patient as able to perform the test.
125-037	Unable to perform exercise test. The coordinator note says “shortness of breath.” We concluded that the patient met criteria as they were on the treadmill and data was obtained. We rated this patient as able to perform the test.
221-073	Was on the treadmill although couldn't keep up. Not on beta blockers. We concluded that the patient met criteria as they were on the treadmill and data was obtained. We rated this patient as able to perform the test.

Table 5 lists other miscellaneous concerns noted during the review.

Table 5. Other Concerns Regarding Participant Eligibility	
Participant ID	**Comments**
236-081	The patient died during study. As per our review, this subject was ineligible. It was noted that he was unable to perform the stress test as he walked with a cane. The patient was randomized and received active study drug. Patient was rated as a study drop after his death on 4/30/2010. The last follow-up on study was a week 4 phone call on 4/22/10. On week 5, the study team found out that the patient was dead due to a significant renal disease (cr = 3.4 in October of 2009). There was a discussion of putting the patient on dialysis during their participation in the study.
296-096	Patient is eligible. However, he received a prescription for Lexapro from Dr. Jiang at his primary endpoint visit. Lexapro is also the study drug (i.e., escitalopram). Blind was broken for all study subjects when the last subject completed the last primary endpoint. There is also no information on when the patient was supposed to fill the prescription.
350-114	The CDU (Cardiac Diagnostic Unit) flowsheet is missing at baseline. The entire folder for the baseline EKG is missing, but eligibility criteria and ECHO interpretation are mentioned in CRC note which is why we are marking this subject eligible.

PROTOCOL VIOLATIONS

It was noted that 6 manuscripts have been published using data from those patients (N=307) who completed the baseline eligibility assessment. However, the approved protocol or informed consent form (ICF) does not state that this baseline assessment data, among those patients who do not go on to participate in the REMIT RCT, will be used in this manner. Moreover, the most recent published manuscript reviewed (published in 2017) reported annual longitudinal findings from this baseline sample for a median of four years. Information collected included patient's medical status, hospitalizations, and current use of antidepressant medication. For patients who could not be reached after 3 telephone call attempts, information was gathered from medical records. This publication also states that "The study protocol was reviewed and approved by the Duke Institutional Review Board, and all participants provided written informed consent." However, this schedule of assessments is not listed in the approved protocol or the study informed consent form (ICF). Again, the ICF only outlines a schedule of events for those patients who participate in the REMIT RCT.